Review

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"Oldie But Goodie": Pediatric Clinical Concepts

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ABSTRACT

In this review five older and lesser known clinical concepts which have weathered decades of clinical practice are presented along with the best supportive evidence that is currently available. Parenteral diarrhea is defined as diarrhea due to infections outside the gastrointestinal tract; and specifically, urinary tract infections are often associated with concomitant diarrhea. The otitis-conjunctivitis syndrome is a clinical observation that for specific infectious agents otitis media and conjunctivitis will commonly occur together. The concept of double-sickening; a potentially useful clinical presentation that commonly forecasts a secondary bacterial infection is also reviewed. Another lesser known topic discussed is the evidence that Candida species frequently colonize the skin in many diaper rashes and the early and more liberal administration of antifungal medications may be appropriate. Finally, in contrast to the common practice of aggressively treating fever, there is new and growing evidence suggesting that fever is actually beneficial to the patient. While these five older clinical concepts have variable degrees of supporting evidence, their longevity and usefulness over decades of clinical practice cannot be denied.

KEY WORDS: Otitis-conjunctivitis syndrome; Fever; Parenteral diarrhea; Double sickening; Diaper dermatitis; Antipyretics; Otitis media; _Candida albicans._

INTRODUCTION

In this article, we present several useful older clinical concepts which may be unfamiliar to many clinicians. Nevertheless, there are a number of "oldie but goodie" clinical concepts that are helpful in the practice of pediatric medicine. In fact, some of these concepts showed up for the first time in the medical literature nearly a century ago. Unfortunately, the evidence supporting most of these clinical entities is limited and often of poor quality. Consequently, one should feel free to question the validity of these older, less evidence based clinical concepts that are usually not at the forefront of medical education. Our clinical experience; however, suggests that the concepts discussed in the article are bona fide, valuable and useful in the practice of emergency medicine.

PARENTERAL DIARRHEA

The concept of parenteral diarrhea has been around for at least a century[1-3]; however, it is often not recognized, acknowledged or discussed as an important clinical entity. Parenteral diarrhea is defined as diarrhea due to infections outside the gastrointestinal tract. The pathophysiology is unclear, but infections elsewhere in the body such as otitis media[4,5] or more frequently urinary tract infections are sometimes associated with diarrhea.[6-8] The diarrhea pattern, however, is characteristically different from the patterns commonly seen with gastrointestinal diseases. Parenteral diarrhea is typically only 2-3 loose stools per day rather than 5 to 10 watery stools seen with most acute gastroenteritis (AGE). Parenteral diarrhea will often occur in the context

of occasional vomiting and or fever, and, the other signs of a urinary tract infection may be absent.[6] Consequently, because of the diarrhea, the presentation is frequently labeled as a viral gastroenteritis and the associated infections are not sought out. In our experience, urinary tract infections appear to be the most commonly associated infection that presents as a parenteral diarrhea. Of concern is the fact that approximately 60% of first time urinary tract infections in children have evidence of upper tract disease or pyelonephritis.[9,10] This association with diarrhea can serve as the proverbial red herring that distracts the clinician from searching further for the actual fever source. While the concept of parenteral diarrhea is admittedly not on the forefront of clinical teaching and was first discussed in the older medical literature, it is not without some respect and can be found in reputable pediatric textbooks.[11]

OTITIS-CONJUNCTIVITIS SYNDROME

Another older clinical concept that seems to be less commonly taught or discussed is the otitis-conjunctivitis syndrome. The association of otitis media and conjunctivitis has been described since the early 1980's.[12,13] What is unique about the otitis-conjunctivitis syndrome is the temporal association of the two infections and the infectious agent which is most commonly nontypable strains of *Hemophilus influenzae*.[12-17] Typically, the same strain of *H.influenzae* is found in both the eyes and the ears.[15] In our experience sinusitis is also part of this association but does not seem to be widely discussed.[18] The otitis-conjunctivitis syndrome can almost be diagnosed from across the room. These children tend to have impressive amounts of purulent drainage from their reddened eyes and when the ears are examined they will typically be infected. The amount of purulent drainage, eye crusting and eye gluing are consistently more dramatic than seen with the vast majority of viral eye infections (Figure 1). Frequently, in our experience, a history consistent with sinusitis such as nasal drainage greater than 10 days is often associated.[18] Treatment options include oral antibiotics with ß-lactamase stability such as amoxicillin/clavulanate or cefdinir which are appropriate antibiotics for the otitis media and associated sinusitis.[15,19] While it may not be necessary for the patient taking oral antibiotics, if you decide to treat the conjunctivitis topically,

polymyxi B/trimethoprim provides reasonable coverage against the ocular pathogens.[14]

"DOUBLE SICKENING"

The term "double sickening" is currently used most often in the diagnosis of sinusitis.[19-21] Double sickening is a phenomenon presenting as a biphasic illness. Historically it has been used for any clinical setting where the patient with a respiratory tract infection is apparently improving or stable and then suddenly worsens.[22] While sinusitis commonly presents with "double sickening", otitis media and bacterial pneumonia also presents with this clinical pattern.[19] Otitis media and sinusitis are recognized to be commonly associated complications of upper respiratory tract infections.[18] Typically these patients have three to four days of an upper respiratory tract from which they often appear to be recovering. Then unexpectedly, there is the onset of a fever and the patient appears and feels sicker. Most clinicians will respond appropriately to this clinical scenario and look for a secondary bacterial infection without acknowledging this older clinical label. Nevertheless, the "double sickening" presentation is potentially a valuable clue that should prod the clinician to investigate for a secondary bacterial pneumonia, otitis media or sinusitis.

EARLY ANTI-FUNGAL TREATMENT OF DIAPER DERMATITIS

Diaper dermatitis (DD) is inflammation and irritation of skin covered by a diaper and results from exposure to moisture from urine and feces in an occlusive environment as well as friction between the diaper material and the skin of the perianal and perineal areas.[23] The prevalence is estimated to be between 7% and 35%[23] and diaper dermatitis represents the most common skin condition of infancy.[24] Though unsettling to parents, DD generally resolves within a few days without therapy, but protracted cases are potentially more complicated with concern for superinfection with either fungus or bacteria.[23-26]

In 1971, Montes et al cultured the diaper areas of 35 patients with diaper dermatitis and 25 patients with healthy skin; *Candida albicans* was recovered from 27/35 (77%) of the pa-

Figure 1: Toddler with Otitis-Conjunctivitis Syndrome and Nasal Drainage for Two Weeks.

tients with DD and only 3/25 (12%) of the controls.[26] According to Weston et al in 1980, *Candida albicans* frequently complicates diaper dermatitis which has persisted for longer than 3 days, and the authors noted that the rash may not exhibit the typical candidal pattern with satellite lesions.[25] Nearly 40 years ago, they advocated for liberal use of anti-fungal medications in cases of diaper dermatitis which persisted for longer than three days.[25]

Many subsequent articles have supported this theory that *Candida albicans* is a frequent contaminant of diaper dermatitis. Ferrazzini et al reported that colonization with Candida species occurred significantly more frequently in children with diaper dermatitis compared to children with normal skin (perianal 75% *vs.* 19%; inguinal 50% *vs.* 10%; oral 68% *vs.* 25%, $p<0.0003$).[28] Gupta et al noted that the number of Candida yeasts in normal skin in the diaper area is very low, and yeasts are isolated in fewer than 4% of cases.[29] Lopez Martinez et al reported the frequency of Candida species in 140 children between birth and 20 months who presented with diaper rash. In that study, 65.7% of the isolates from the affected skin were Candida species.[30] Gokalp et al observed that in 40 patients with DD, *Candida albicans* was isolated in 37; in the 20 control patients with normal diaper area skin, there was no *Candida albicans* cultured.[31] Finally, Dorko et al evaluated 60 children 1 to 15 months of age with diaper dermatitis and found that Candida species were isolated from the skin of all 60 children with *Candida albicans* accounting for 41/60.[32] The authors also mentioned that the use of disposable diapers decreases the total incidence of diaper dermatitis.

In summary, *Candida albicans* is frequently isolated from the skin of infants with diaper dermatitis while it is rarely isolated from normal controls, suggesting that while it may not instigate diaper dermatitis, it probably plays a role in aggravating pre-existing diaper rash and could certainly explain persistence of diaper dermatitis beyond the usual 1 to 2 day course. Given this information, it is more likely than not that diaper rash that has continued longer than 72 hours may be colonized with *Candida albicans* and in addition to barrier protection the addition of anti-fungal medications should be considered in its management.

FEVER BENEFITS

As long as people have studied and practiced medicine, fever has been recognized as one of the earliest harbingers of illness. While we now know fever to be a product of a complex interaction of multiple different cytokines, it has long been discussed as to whether it is more than just a sign of illness. Specifically, is fever beneficial to the body and part of a natural healing process or something harmful that should be aggressively eradicated? While several different species of both warm-blooded and cold blooded animals are capable of producing a fever when exposed to infectious microorganisms, humans are the only ones who go out of their way to suppress a fever. The discussion has gone on for decades and while much of the literature is older and the evidence is not of the highest quality, the general consensus of

evidence is that fever does have therapeutic benefits.[33] It is also acknowledged that fever appears to be detrimental in some clinical populations.[34] Fever is a hypermetabolic state which increases metabolic demand and oxygen consumption in organs such as the brain and the heart and worsens pre-existing disease.[33] It is also associated with increased insensible fluid loss and risk of dehydration, febrile seizures, metabolic acidosis, tachycardia, anorexia, and body discomfort. Nevertheless, guidance for the clinicians by the American Academy of Pediatrics (AAP) in 2011 states unequivocally that fever is a physiologic mechanism that has beneficial effects in fighting infection.[35] This statement iterates that there is no evidence that fever itself worsens the course of an illness or that it causes long-term neurologic complications. The primary goal of treating the febrile child should be the child's overall comfort rather than the normalization of body temperature.[35]

Fever has purposely been induced for therapeutic intentions and one of the early pioneers of this therapy was a 1917 Nobel award winning psychiatrist, Wagner-Jauregg. Fever therapy was used by Dr. Wagner-Jauregg to treat psychiatric illness and neurosyphilis. He induced high fevers in his target patients by injecting them with blood from malaria patients.[36,37] Some of his patients appeared to respond to the high fevers while a few actually died due to the virulent strain of malaria injected. Additionally, there is evidence that fever has a number of physiologic actions that appear to improve immune responses to infections.[38-40] In terms of survival in the animal models the advantages of fever are well founded.[41] Animal models including sheep, rats, and ectothermic desert lizards have shown evidence of fever associated survival benefit from sepsis, peritonitis or influenza infections. For example, Su et al injected 0.5 g/kg body weight of feces into the abdominal cavity to induce sepsis in 24 fasted, anesthetized, invasively monitored, mechanically ventilated female sheep. The administration of acetaminophen and external cooling lowered protective HSP70 (Heat Shock Protein) concentrations as well as demonstrated negative effects on respiratory function, higher blood lactate concentrations and shortened survival times.[40] Another representative example is a meta-analysis of eight studies of influenza-infected animals that reported an increased risk of mortality when the animals were treated with antipyretics.[42]

However, this discussion will not attempt to reiterate in detail the animal studies as there are multiple other articles and reviews that discuss these in greater detail.[42-48] Instead, we will present some of the most compelling research involving humans. While the research is mostly in adult patients, it is most likely that the pediatric patient will have similar physiologic responses to fever.

While there are fewer papers discussing benefits of fever for humans, significant relevant research is available. Human evidence can be categorized in the following types of studies and outcomes: 1. Antipyretics have no apparent positive or negative affect 2. Fever is associated with improved survival. 3. Antipyretics are associated with decreased survival. 4. Anti-

pyretics prolong viral shedding or malaria clearance time. Examples of each category will be presented.

Antipyretics have no Apparent Positive or Negative Effect

In a randomized study of 700 consecutive patients with fever early administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days.[49] However, axillary temperatures were used in the study and on days 3 through 7 the documented mean daily peak body temperature was nearly identical in the acetaminophen group and the placebo group as was the mean daily average body temperature.[50] Nevertheless, fever did not have a negative effect on outcomes in this study. Bernard et al reported a randomized, controlled trial of 455 septic patients. In this study treatment of fever in sepsis patients reduced inflammatory factors, fever, tachycardia, oxygen consumption and lactic acidosis, but it did not prevent the development of shock, acute respiratory distress syndrome and did not improve survival.[51] Again, the presence of fever also did not appear to decrease survival in the septic patients.

Fever is Associated with Improved Outcomes or Survival

Peres Bota et al reported in 2004 that patients with septic shock had a higher mortality if they were hypothermic than if they were febrile (80 *vs*. 50%, *p*<0.01) although normothermic patients had significantly better survival.[52] A 2009 study by Leroy et al demonstrated that fever >38.2 °C was associated with a greater survival frequency in invasive *Candida spp*. infections in the ICU.[53] In a 2017 meta-analysis of 42 studies by Rumbus et al fever predicted lower mortality rates while hypothermia showed higher mortality rates compared with normal body temperature.[54] This study included a total of 10,834 septic patients and 2,724 deaths. Septic patients with the lowest chance of mortality (<25%) had higher body temperatures than those with the highest chance of dying (>75%).[54] Finally, a 2017 observational cohort study of 2,225 septic patients by Sundén-Cullberg found that increased body temperature in the emergency department was strongly associated with lower mortality and shorter hospital stays in patients with severe sepsis or septic shock subsequently admitted to the ICU.[55] In that study mortality was inversely correlated with temperature and decreased, on average, more than 5 percentage points per degree Centigrade increase, from 50% in those with the lowest temperatures to 9% in those with the highest.[55]

Antipyretics are Associated with Decreased Survival

Schulman et al reported a small study describing aggressive treatment of fever with cooling and acetaminophen in febrile ICU patients and the study was stopped after the first interim analysis due to the mortality difference.[56] Their conclusion was that aggressively treating fever in critically ill patients may lead to a higher mortality. A prospective observational study by Lee et al of 1,425 consecutive critically ill adult patients (antipyretic treatment was given 4,863 times to 737 patients or 51.7%) reported for septic patients that the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen was independently associated with increased mortality and fever was not associated with mortality.[57] For non-septic patients; however, high fever (≥39.5 °C) was independently associated with mortality.[57] A 2017 study by Ye et al reported that the use of antipyretics was associated with increased risk of mortality in septic ICU patients requiring mechanical ventilation and that external cooling was also deleterious.[58]

Antipyretics Prolong Viral Shedding or Malaria Clearance Time

Other evidence exists that causes one to pause in regards to the administration of antipyretics. Doran et al performed a randomized, double-blind study to determine whether or not acetaminophen affects the duration or severity of childhood varicella.[59] The conclusion of this study was that acetaminophen did not alleviate symptoms in children with varicella and actually appeared to prolong illness.[59] Brandts et al performed a randomized study of the effect of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. Their study found that paracetamol prolonged parasite clearance time possibly by decreased production of tumor necrosis factor (TNF) which has antiparasitic properties and oxygen radicals that are part of the immune cascade.[60] In two double-blind trials by Stanley et al volunteers infected with rhinovirus were treated with aspirin or placebo. Aspirin treatment was associated with a moderate reduction in the frequency or severity of some symptoms, but aspirin treatment appeared to cause a highly significant increase in the rate of virus shedding in treated subjects.[61] The authors commented that this increase in virus shedding could potentially influence the course of the disease as well as increase the spread of the infection to contacts.[61] Finally, Graham et al performed a double-blind, placebo-controlled trial of the effects of over-the-counter analgesic/antipyretic medications on virus shedding, immune response, and clinical status in the common cold.[62] Sixty volunteers were challenged with intranasal rhinovirus type 2 and were randomized to treatment arms of aspirin, acetaminophen, ibuprofen or placebo. The use of aspirin and acetaminophen was associated with increased nasal symptoms and signs as well as suppression of serum neutralizing antibody response. Also, while not statistically significant, there was a trend in the aspirin and acetaminophen groups toward longer duration of virus shedding.[62]

While fever overall appears beneficial, it is also important to acknowledge that fever has its associated costs. Mistry et al documented those costs and concluded that febrile illnesses have considerable effects on the child, caregivers, and families after emergency department (ED) evaluation.[63] Additionally, higher, persistent fevers will often result in return visits to the ED.[64] Nevertheless, there appears to be sufficient evidence, albeit with some limitations, to justify teaching our parents and healthcare providers in training that for the vast majority of our patients the presence of fever appears to be beneficial to the patient and does not need to be aggressively managed.

CONCLUSION

In this article we presented five older clinical concepts that do not appear to be on the forefront of clinical knowledge or backed with extensive high quality research. Nevertheless, these clinical teachings appear to have weathered decades of clinical practice and based on the available evidence and clinical experience appear to be valid and clinically valuable.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.
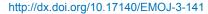
CONSENT

We have signed permission from the parents of the child.

REFERENCES

1. Cox MA. A statistical study of fermentative diarrhoea, infectious diarrhoea, acute intestinal intoxication and decomposition occurring in the hospital for sick children, from October 1st, 1919, to October 1st, 1920, considering especially the relation of age, weight and parenteral infections to mortality. *Can Med Assoc J*. 1922; 12(8): 554-558.

2. Scott TFM, Gunn W, Gairdner P, Andrewes CH, Mitman M, Gale AH. Discussion on parenteral diarrhoea. *Proc R Soc Med*. 1944; 37(9): 479-482.

3. Ariztia A, Garces C. Acute diarrhea in infancy. *Pediatrics*. 1948; 2(5): 525-32.

4. Rabbiner, Max. Otitic infection with gastroenteritis in infants. *Laryngoscope*. 1933; 43(4): 274-279. doi: 10.1288/00005537-193304000-00003

5. DeSanctis AG, Larkin VD. Otitis media and mastoiditis in children, a survey of 1,992 cases. *JAMA*. 1942; 120(14): 1087-1093. doi: 10.1001/jama.1942.02830490007002

6. Thakar R, Rath B, Prakash SK, Mittal SK, Talukdar B. Urinary tract infection in infants and young children with diarrhea. *Indian Pediatr*. 2000; 37(8): 886-889.

7. Fallahzadeh MH, Ghane F. Urinary tract infection in infants and children with diarrhoea. *East Mediterr Health J*. 2006; 12(5): 690-694.

8. Narayanappa D, Rajani HS, Sangameshwaran A. Study of urinary tract infection in infants and young children with acute diarrhea. *Indian J Public Health*. 2015; 6(2): 226-229.

9. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: A systematic review. *Pediatrics*. 2010; 126(6): 1084-1091. doi: 10.1542/peds.2010-0685

10. Pecile P, Miorin E, Romanello C, et al. Age-related renal parenchymal lesions in children with first febrile urinary tract infections. *Pediatrics*. 2009; 124(1): 23-29.

11. Pereira F, Hsu D. Diarrhea. In: Fleisher GR, Ludwig S, eds, *Textbook of Pediatric Emergency Medicine*. 7th ed. Philadelphia, PA, USA: Lippincott Williams & Wilkins; 2016: 135-139.

12. Bodor FF. Conjunctivitis-otitis syndrome. *Pediatrics*. 1982; 69(6): 695-698.

13. Bodor FF, Marchant CD, Shurin PA, Barenkamp SJ. Bacterial etiology of conjunctivitis-otitis media syndrome. *Pediatrics*. 1985; 76(1):26-28.

14. Block SL, Hedrick J, Tyler R, et al. Increasing bacterial resistance in pediatric acute conjunctivitis (1997-1998). *Antimicrob Agents Chemother*. 2000; 44(6): 1650-1654. doi: 10.1128/AAC.44.6.1650-1654.2000

15. Bingen E, Cohen R, Jourenkova N, Gehanno P. Epidemiologic study of conjunctivitis-otitis syndrome. *Pediatr Infect Dis J*. 2005; 24(8): 731-732.

16. Buznach N, Dagan R, Greenberg D. Clinical and bacterial characteristics of acute bacterial conjunctivitis in children in the antibiotic resistance era. *Pediatr Infect Dis J*. 2005; 24(9): 823-828.

17. Palmu AA, Herva E, Savolainen H, Karma P, Mäkelä PH, Kilpi TM. Association of clinical signs and symptoms with bacterial findings in acute otitis media. *Clin Infect Dis*. 2004; 38(2): 234-242. doi: 10.1086/380642

18. Revai K, Dobbs LA, Nair S, Patel JA, Grady JJ, Chonmaitree T. Incidence of acute otitis media and sinusitis complicating upper respiratory tract infection: The effect of age. *Pediatrics*. 2007; 119(6): e1408-e1412.

19. Chow AW, Benninger MS, Brook I, et al. Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. 2012; 54(8): e72-e112. doi: 10.1093/cid/cir1043

20. Libman H, Brockmeyer DM, Gold HS. Should we prescribe antibiotics to this patient with persistent upper respiratory symptoms? Grand rounds discussion from beth Israel Deaconess Medical Center. *Ann Intern Med*. 2017; 166(3): 201-208. doi: 10.7326/M16-2766

21. Harris AM, Hicks LA, Qaseem A; High Value Care Task Force of the American College of Physicians and for the Centers for Disease Control and Prevention. Appropriate antibiotic use for acute respiratory tract infection in adults: Advice for high-

value care from the American College of Physicians and the Centers for Disease Control and Prevention. *Ann Intern Med*. 2016; 164(6): 425-434. doi: 10.7326/M15-1840

22. Gor N, Mintz M. Sinusitis. In: Mintz ML, ed, *Disorders of the Respiratory Tract, Common Challenges in Primary Care*. New York City, NY, USA: Humana Press Inc.; 2006: 65-76.

23. Bonifaz A, Rojas R, Tirado-Sánchez A, et al. Superficial mycoses associated with diaper dermatitis. *Mycopathologia*. 2016; 181(9-10): 671-679. doi: 10.1007/s11046-016-0020-9

24. Ward DB, Fleischer AB Jr, Feldman SR, Krowchuk DP. Characterization of diaper dermatitis in the United States. *Arch Pediatr Adolesc Med*. 2000; 154(9): 943-946. doi: 10.1001/archpedi.154.9.943

25. Weston WL, Lane AT, Weston JA. Diaper dermatitis: current concepts. *Pediatrics*. 1980; 66(4): 532-536.

26. Montes LF, Pittillo RF, Hunt D, Narkates AJ, Dillon HC. Microbial flora of infant's skin. Comparison of types of microorganisms between normal skin and diaper dermatitis. *Arch Dermatol*. 1971; 103(4): 400-406. doi: 10.1001/archderm.1971.04000180066009

27. Leyden JJ, Kligman AM. The role of microorganisms in diaper dermatitis. *Arch Dermatol*. 1978; 114(1): 56-59. doi: 10.1001/archderm.1978.01640130020006

28. Ferrazzini G, Kaiser RR, Hirsig Cheng SK, et al. Microbiological aspects of diaper dermatitis. *Dermatology*. 2003; 206(2): 136-141. doi: 10.1159/000068472

29. Gupta AK, Skinner AR. Management of diaper dermatitis. *Int J Dermatol*. 2004; 43(11): 830-834. doi: 10.1111/j.1365-4632.2004.02405.x

30. LópezMartínez R, Ruiz-Maldonado R. Candidiasis in children with diaper rash. Study of 140 cases. *Med Cutan Ibero Lat Am*. 1982; 10(4): 225-230.

31. Gökalp AS, Aldirmaz C, Oğuz A, Gültekin A, Bakici MZ. Relation between the intestinal flora and diaper dermatitis in infancy. *Trop Geogr Med*. 1990; 42(3): 238-240.

32. Dorko E, Virágová S, Pilipcinec E, Tkáciková L. Candida-agent of the diaper dermatitis? *Folia Microbiol (Praha)*. 2003; 48(3): 385-388. doi: 10.1007/BF02931371

33. Launey Y, Nesseler N, Mallédant Y, Seguin P. Clinical review: Fever in septic ICU patients—friend or foe? *Crit Care*. 2011; 15(3): 222. doi: 10.1186/cc10097

34. Nielsen N, Wetterslev J, Cronberg T, et al; TTM Trial Investigators. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. *N Engl J Med*. 2013; 369(23): 2197-2206. doi: 10.1056/NEJMoa1310519

35. Sullivan JE, Farrar HC. Fever and antipyretic use in children. Section on Clinical Pharmacology and Therapeutics; Committee on Drugs. *Pediatrics*. 2011; 127(3): 580-587. doi: 10.1542/peds.2010-3852

36. Whitrow M. Wagner-Jauregg and fever therapy. *Med Hist*. 1990; 34(3): 294-310.

37. Blumenthal I. Fever—concepts old and new. *J R Soc Med*. 1997; 90(7): 391-394.

38. Ryan M, Levy MM. Clinical review: Fever in intensive care unit patients. *Crit Care*. 2003; 7(3): 221-225. doi: 10.1186/cc1879

39. Roberts NJ Jr. Impact of temperature elevation on immunologic defenses. *Rev Infect Dis*. 1991; 13(3): 462-472. doi: 10.1186/cc1879

40. Su F, Nguyen ND, Wang Z, Cai Y, Rogiers P, Vincent JL. Fever control in septic shock: Beneficial or harmful? *Shock*. 2005; 23(6): 516-520.

41. Avner JR. Acute fever. *Pediatr Rev*. 2009; 30(1): 5-13; quiz 13. doi: 10.1542/pir.30-1-5

42. Eyers S, Weatherall M, Shirtcliffe P, Perrin K, Beasley R. The effect on mortality of antipyretics in the treatment of influenza infection: Systematic review and meta-analysis. *J R Soc Med*. 2010; 103(10): 403-411. doi: 10.1258/jrsm.2010.090441

43. Plaisance KI, Kudaravalli S, Wasserman SS, Levine MM, Mackowiak PA. Effect of antipyretic therapy on the duration of illness in experimental influenza A, Shigellasonnei, and Rickettsia rickettsii infections. *Pharmacotherapy*. 2000; 20(12): 1417-1422. doi: 10.1592/phco.20.19.1417.34865

44. Sunden Y, Park CH, Matsuda K, et al. The effects of antipyretics on influenza virus encephalitis in mice and chicks. *J Vet Med Sci*. 2003; 65(11): 1185-1188. doi: 10.1164/arrd.1984.130.5.857

45. Esposito AL. Aspirin impairs antibacterial mechanisms in experimental pneumococcal pneumonia. *Am Rev Respir Dis*. 1984; 130(5): 857-862. doi: 10.1164/arrd.1984.130.5.857

46. Vaughn LK, Veale WL, Cooper KE. Antipyresis: Its effect on mortality rate of bacterially infected rabbits. *Brain Res Bull*. 1980; 5(1): 69-73. doi: 10.1016/0361-9230(80)90285-3

47. Bernheim HA, Kluger MJ. Fever: Effect of drug-induced antipyresis on survival. *Science*. 1976; 193(4249): 237-239.

48. Kurosawa S, Kobune F, Okuyama K, Sugiura A. Effects of

antipyretics in rinderpest virus infection in rabbits. *J Infect Dis*. 1987; 155(5): 991-997. doi: 10.1126/science.935867

49. Young P, Saxena M, Beasley R. Acetaminophen for fever in critically ill patients with suspected infection. *N Engl J Med*. 2016; 374(13): 1292-1293. doi: 10.1056/NEJMoa1508375

50. Young P, Saxena M, Bellomo R; HEAT Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Acetaminophen for Fever in Critically Ill Patients with Suspected Infection. *N Engl J Med*. 2015; 373(23): 2215-2224. doi: 10.1056/NEJMoa1508375

51. Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med*. 1997; 336(13): 912-918. doi: 10.1056/NEJM199703273361303

52. Peres Bota D, Lopes Ferreira F, Mélot C, Vincent JL. Body temperature alterations in the critically ill. *Intensive Care Med*. 2004; 30(5): 811-816. doi: 10.1007/s00134-004-2166-z

53. Leroy O, Gangneux JP, Montravers P, et al; Amar Cand Study Group. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: A multicenter, prospective, observational study in France (2005-2006). *Crit Care Med*. 2009; 37(5): 1612-1618. doi: 10.1097/CCM.0b013e31819efac0

54. Rumbus Z, Matics R, Hegyi P. Fever is associated with reduced, hypothermia with increased mortality in septic patients: A meta-analysis of clinical trials. *PLoS One*. 2017; 12(1): e0170152. doi: 10.1371/journal.pone.0170152

55. Sundén-Cullberg J, Rylance R, Svefors J, Norrby-Teglund A, Björk J, Inghammar M. Fever in the emergency department predicts survival of patients with severe sepsis and septic shock admitted to the ICU. *Crit Care Med*. 2017; 45(4): 591-599. doi: 10.1097/CCM.0000000000002249

56. Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: A randomized, prospective study. *Surg Infect (Larchmt)*. 2005 Winter; 6(4): 369-375. doi: 10.1089/sur.2005.6.369

57. Lee BH, Inui D, Suh GY; Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group. Association of body temperature andantipyretic treatments with mortality of critically ill patients with and without sepsis: Multi-centered prospective observational study. *Crit Care*. 2012; 16(1): R33. doi: 10.1186/cc11211

58. Ye S, Xu D, Zhang C, Li M, Zhang Y. Effect of antipyretic therapy on mortality in critically Ill patients with sepsis receiving mechanical ventilation treatment. *Can Respir J*. 2017; 2017: 3087505. doi: 10.1155/2017/3087505

59. Doran TF, De Angelis C, Baumgardner RA, Mellits ED. Acetaminophen: More harm than good for chickenpox? *J Pediatr*. 1989; 114(6): 1045-1048. doi: 10.1016/S0022-3476(89)80461-5

60. Brandts CH, Ndjavé M, Graninger W, Kremsner PG. Effect of paracetamol on parasite clearance time in Plasmodium falciparum malaria. *Lancet*. 1997; 350(9079): 704-709. doi: 10.1016/S0140-6736(97)02255-1

61. Stanley ED, Jackson GG, Panusarn C, Rubenis M, Dirda V. Increased virus shedding with aspirin treatment of rhinovirus infection. *JAMA*. 1975; 24; 231(12):1248-1251. doi: 10.1001/jama.1975.03240240018017

62. Graham NM, Burrell CJ, Douglas RM, Debelle P, Davies L. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J Infect Dis*. 1990; 162(6): 1277-1282. doi: 10.1093/infdis/162.6.1277

63. Mistry RD, Stevens MW, Gorelick MH. Short-term outcomes of pediatric emergency department febrile illnesses. *Pediatr Emerg Care*. 2007; 23(9): 617-623. doi: 10.1097/PEC.0b013e318149f639

64. Klein-Kremer A, Goldman RD. Return visits to the emergency department among febrile children 3 to 36 months of age. *Pediatr Emerg Care*. 2011; 27(12): 1126-1129. doi: 10.1097/PEC.0b013e31823a3e86