Heparinization of Long Indwelling Lines in Neonates: Systematic Review and Practical Recommendations

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ABSTRACT: Prolonged vascular access is an essential element in the care of most critically ill and premature neonates. However, the role of prophylactic heparinization in achieving this remains controversial. The aim of this paper is to provide practical recommendations based on a systematic review of the literature on prophylactic heparinization by continuous infusion in indwelling long lines in preterm neonates. All randomized controlled trials, and non-randomized case-control studies, looking at heparin vs. no heparin in neonates were included. We concluded that the literature supports heparinization to prolong longevity of long lines. We then compared dosing vs. efficacy to determine optimal dosage recommendations, which we suggest to be 10–50 IU/kg/day. Finally, we devised a practical clinical aid which calculates the heparin exposure at various birth weights, infusion rates and heparin dosages in order to facilitate easy bedside determination as to which combination best meets the recommendations.

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Prolonged vascular access is an essential element in the care of most critically ill and premature neonates. However, indwelling long lines often become occluded and need to be removed. Furthermore, the incidence of catheter-related thrombosis in neonates is probably much higher than generally considered. In a review of central line thromboses Revel-Vilk and Ergaz [1] reported that umbilical artery catheters (UAC) thrombosis was found on autopsy in 59% of infants, whereas ultrasound demonstrated UAC thrombosis in only ~25% of neonates; UVC thrombosis was found on autopsy studies in up to 65% of infants, whereas ultrasound screening for thrombosis showed a rate of 22–43%. A retrospective large cohort of 882 infants with 1540 PICCs reported occurrence of clinical thrombosis (cord, phlebitis, extremity edema, extremity perfusion, and inability to draw or flush the catheter) in 14% of infants [2], while the rate of symptomatic peripherally inserted central catheter (PICC)-related thrombosis confirmed by ultrasound was reported at a significantly lower frequency (< 1.5%).

Studies have shown that heparinization of these lines can prolong their longevity [3]. However, heparinization of indwelling long lines in newborn infants has become the subject of intensive reevaluation in recent years. Clinically, we struggle with the most basic of issues –issues such as whether heparinization of indwelling lines is justified or even imperative? If so, for which type of lines and at what dose? And finally, what are the side effects and potential toxicities of heparinization, particularly in the extremely low birth weight population? Some of the controversy lies in the paucity of data and in the different endpoints sought in the existing studies. Some of the studies have looked at the efficacy of heparin in terms of line longevity; others have studied thromboses and/or sepsis prevention. In this paper we present a practical approach to the use of continuous heparinization of indwelling long lines which is based on a systematic review of these controversial issues. The criteria used for considering studies for this review were:

- **Types of studies**: All trials using random or quasi-random or retrospective patient allocation
- **Types of participant:** Premature infants who received continuous heparin infusion for the maintenance of PICC lines or umbilical lines
- **Types of interventions:** The use of continuous heparin infusion vs. placebo for the maintenance of central lines
- **Types of outcome measures**: The primary outcome of interest was the longevity of central lines. Secondary outcomes included rates of hemorrhagic complications, intraventricular hemorrhage and sepsis.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

We searched the following databases: Medline, OVID, Google Scholar, and The Cochrane Library. The key words for the search were: heparin, guidelines, umbilical catheter, PICC, and percutaneous central venous catheter (PCVC). The search applied to publications from 1980 to 2015. We limited the search to neonates and to continuous heparin infusions. Levels of evidence and grades were defined according to the classification of the Oxford Centre for Evidence based Medicine and are recorded in the appropriate tables. The authors assessed the risk of bias of individual studies

(e.g., adequacy of randomization, blinding, completeness of follow-up). The principal summary measure was the risk ratio for catheter occlusion.

Using the above keywords in a Medline search, 151 references were retrieved of which 36 were potentially relevant. Three of these were earlier versions of reviews that were subsequently updated and the most recent versions were included. One study was published in Chinese and we had access only to the English abstract. Two studies were retrospective reviews rather than randomized prospective trials. In Google Scholar, a similar search retrieved 85 references, of which 25 were potentially relevant. Others were eliminated because they did not include line longevity data, they dealt with intermittent flushes rather than continuous infusions, or they compared different catheter types or insertion sites. In addition, we searched references cited in relevant articles. We limited the search to neonates and to continuous heparin infusions (i.e., to the exclusion of lines treated with heparin flushes, studies dealing with routine peripheral intravenous infusions, and studies of therapeutic heparinization in the treatment of thrombi). Based on our review, we concluded that the current state of the art supports heparinization of long lines in neonates. We then developed a new clinical approach to the administration of heparin in long lines in the Neonatal Intensive Care Unit.

UMBILICAL ARTERY CATHETERS

In a systematic Cochrane review, Barrington [3] documented that heparin infusion effectively decreased the incidence of UAC occlusion although it did not affect the frequency of aortic thromboses. There were no statistically significant adverse outcomes noted. He searched for randomized and quasi-randomized clinical studies of line heparinization in either term or preterm infants and identified and analyzed six randomized controlled trials of which we chose to include four (n=253) [Table 1] [4-7]. We excluded two trials: one study [8] because it looked at continuous heparin infusion vs. intermittent heparin flushes rather than placebo, and a second because it looked exclusively at the effect of heparin on the occurrence of intraventricular hemorrhage and hemostatic variables and did not report data on line longevity. We did, however, include two additional studies although their methodology did not completely match our search criteria. In the Horgan study [7] the randomization was problematic. They compared infants from four neonatal units with different heparin protocols. Again, although not ideal, we elected to include these data because of the overall dearth of meaningful data from well-designed studies.

Table 1. Summary of studies of heparinization of umbilical artery catheters

Study	Population	Heparin dose	Grade of evidence	Catheter occlusion
Ankola [4] 1993	30 infants, not blinded	0.25 IU/ml	1b	2/15 (H) vs. 11/15 (C) RR 0.18 (0.05, 0.68)
David [5] 1981	50 infants, randomized	1.0 IU/ml	1b	3/23 (H) vs. 15/26 (C) RR 0.23 (0.07, 0.68)
Rajani [6] 1979	62 infants, randomized	1.0 IU/ml	1b	4/32 (H) vs. 19/30 (C) RR 0.20 (0.08, 0.51)
Horgan [7] 1987	111 infants, quasi-randomized	0.46–3.4 IU/kg/hr	3a	2/59 (H) vs. 10/52 (C) RR 0.18 (0.04, 0.77)

H = heparin, C = control, RR = relative risk

We calculated the overall relative risk (RR) of umbilical catheter occlusion prior to removal to be 0.18 (0.09, 0.32, $P < 0.001$). These studies are summarized in Table 1.

PICC LINES/UMBILICAL VENOUS CATHETERS

Previous studies have differentiated between peripherally inserted central venous catheter (PICC lines) and umbilical catheters. Randolph et al. [9] found that heparin (administered intermittently or as a continuous infusion) was effective in the prevention of peripheral arterial catheter complications but not for venous catheter complications. It can be hypothetically argued that data derived from umbilical artery catheters cannot be directly extrapolated to PICC lines, as the size of the catheters (internal diameter) used for umbilical arterial access is larger than that used for PICC placement. In addition, the more rapid flow patterns in the aorta, where umbilical arterial catheters are usually placed, differ from the relatively sluggish circulatory states of the venous system in which PICC lines are placed, thus potentially rendering PICC lines at even higher risk for occlusion.

As such, a series of studies looking specifically at heparinization of PICC lines has been published and analyzed in a Cochrane review [10]. This review identified four relevant randomized trials. Three of these trials [11-13] were determined to be of adequate methodology to meet the eligibility criteria. We identified and included four additional studies published after the Cochrane review [14-17] [Table 2].

The Betremieux study was excluded from the Cochrane review [10] because of methodological flaws. In this study, the infants were randomized to heparin or control at the time of insertion of umbilical catheters. If they later needed a PICC line, they were kept in the original treatment group without further randomization. Four infants had multiple catheter insertions and separate data were not available for the first catheter. Given the theoretical difficulties with the Betremieux study described above, we excluded it from our analysis as well. Heparin significantly reduced the risk of catheter occlusion ($P < 0.0001$). Despite the overall reduced risk of catheter occlusion, there was no statistically significant difference in the duration of catheter patency. This could be due to a higher incidence of elective catheter removals in neonates with completion of therapy in the heparin group (63% vs. 42%, $P = 0.002$). There were no statistically significant differences in the risk of thromboses [RR 0.93, 95% confidence interval (95%CI)

Table 2. Summary of PICC line heparinization studies

Study	Population	Heparin dose	Grade of evidence	Outcome
Shah [11] 2007	Multicenter (4 NICUs) H: n=100 C: n=101	0.5 IU/kg/hr	1b	Catheter occlusion: 6 vs. 31% (P = 0.001) Elective catheter removal after therapy completed: 63 (H) vs. 42% (C) (P = 0.002) Increased duration of catheter usability in the heparin group (P < 0.005)
Birch [12] 2010	H: n=118 C: n=125	0.5 IU/ml	1b	Catheter occlusion: 5/118 (H) vs. 3/125 (C) RR 1.76 (0.48–6.56) (P = 0.42) Reduction in incidence of catheter-related sepsis
Kamala [13] 2002	H: n=36 C: n=32	1.0 IU/ml	1b	Trend to decreased catheter occlusions (14% vs. 23%, P = 0.4) and increased elective catheter removal after completion of therapy (63% vs. 48%, P = 0.3) in heparin-exposed infants
Klenner [14] 2003	H: n = 145 C: n= 151	0.5 IU/ml	1b	Duration of catheter patency longer in heparin group (33.8 vs. 26.4 hr) (P = 0.001) Outcomes reported per catheter
Uslu [15] 2010	H: n=118 C: n=121	0.5 IU/kg/hr	1b	Duration of catheter patency 12.4 ± 4.5 (H) vs. 9.7 ± 4.0 (C) days (P < 0.0001) Less catheter occlusions with heparin: 23 (19.5%) vs. 55 (45.5%) RR 3.44, 95%CI 1.92–6.44 (P < 0.0001)
Isemann [16] 2012	H: n=189 C: n=188	0.25 IU/ml (if > 100 ml/kg/day) or 0.5 IU/ml (if < 100 ml/kg/day)	3a	Retrospective Heparin minimized occlusion and other complications although median catheter duration and complication rates did not differ
Tang [17] 2011	H: n=83 C: n=40	0.5 IU/ml	3a	Retrospective Catheter obstruction (5% vs. 20%), catheter-tip colonization (2% vs. 18%), and CLABSI were significantly lower in the heparin (0) group than in the control group (5) (P < 0.05)

PICC = peripherally inserted central venous catheter, H = heparin, C = control, RR = relative risk, 95%CI = 95% confidence interval, CLABSI = central line-associated bloodstream infection

0.58–1.51], catheter-related sepsis (RR 0.82, 95%CI 0.43–1.57), or extension of intraventricular hemorrhage (RR 0.50, 95%CI 0.19–1.28) between the two groups. Studies evaluating the heparinization of PICC lines are summarized in Table 2.

We identified one study that looked at heparinization of umbilical venous catheters. Unal et al. [18] in a prospective study of term neonates infused heparin (n=19) (0.5 IU/ml) or placebo (n=27) at a rate of 1 ml/hr and found no difference in the incidence of thromobosis 1, 3 or 5 days after catheter insertion.

SEPSIS

Studies have shown an association between catheter-related sepsis and thromboses [19]. Thus, it is theoretically possible that heparinization may also reduce the incidence of catheter-related sepsis. This has been reviewed in several studies. Birch and co-authors [12] reported, in a double-blinded study that included 210 infants, a significant reduction in culture-positive catheter-related sepsis in those infants with heparinized lines as compared to those without heparin (P = 0.04, RR 0.57, 95%CI 0.32–0.98). In contrast, other smaller line heparinization studies that reported sepsis as a secondary outcome [11,13] found no difference in the incidence of sepsis with or without heparin. When we combined the data from these three studies, there was a trend towards less sepsis in the heparin-exposed infants which did not reach statistical significance (RR 0.70, 95%CI 0.4–1.1, P = 0.13].

POTENTIAL ADVERSE EFFECTS

There is a theoretical concern regarding a potential increase in the incidence of intraventricular hemorrhage (IVH) secondary to heparin administration [20-23]. In actuality, however, no increase in the appearance of new IVH between the heparin and no-heparin group (RR 0.50, 95%CI 0.19–1.28) was reported by Kamala et al. in 2002 [13] or by Birch et al. in 2010 [12]; Shah and team in 2007 [11] reported no new or extension of hemorrhage in any of their patients. Chang et al. [20] studied the effect of heparin on bleeding tendencies and IVH and also found no effect on the incidence of IVH or on severe IVH (grades 3-4).

HEPARIN DOSE

While some of the literature reports heparin dosing as a concentration (IU/ml), other studies report a total daily dose as IU/kg/day. In order to develop a unified practical approach, existing data must first be transformed into a consistent format. For this purpose, we chose to view the data based on the total daily heparin dose per kilogram.

In five of eight studies reporting the total heparin dose/kg/day, the total daily dose ranged between ~100 and 200 IU/kg/day [Table 3]. In most studies in which the total heparin dose was not reported, heparin was administered at a rate of 1 IU/ml. Assuming that the infants received between 100 and 150 ml/kg/day, we surmise that the total heparin dose in most of these studies was also within the range of 100–150 IU/kg/day.

As can be seen in Table 3, there were four studies that reported a lower mean total daily heparin dose of 12–50 IU/kg/day. Even at these lower doses, heparin was found to prolong catheter patency without significant adverse outcomes. Studies of both PICC lines and umbilical catheters were involved in the high as well as the low dosing regimens.

Table 3. Total daily heparin doses in IU/kg/day (where reported)

	Total daily heparin dose
Chang [20]	100 IU/kg/day
Bosque [8]	80–220 IU/kg/day (mean 120 IU/kg/day)
Kamala [13]	100 IU/kg/day
David [5]	125–200 IU/kg/day
Rajani 6]	100–200 IU/kg/day
Ankola [4]	25–50 IU/kg/day
Horgan [7]	21 IU/kg/day
Shah [11]	12 IU/kg/day
Klenner [14]	30 IU/kg/day

Perhaps the only study that looked specifically at different levels of prophylactic heparin dosing in the neonatal population was that of Moclair and Bates [24]. Heparin at 0.1, 0.25, 0.5 and 1 IU/ml was added to total parenteral nutrition (TPN) infusions delivered through peripheral veins, and the survival time of the infusions was determined. For infusion sites receiving heparinized fluids, the relative risk of failure decreased and the median survival time increased as the heparin concentration increased, with a maximal effect at a heparin concentration of 0.5 IU/ml ($P < 0.001$). No incremental advantage was observed with heparin at doses above 0.5 IU/ml.

Both Cochrane reviews concluded that the prophylactic use of heparin for PICC lines and for umbilical artery catheters allows a greater number of infants to complete their intended use (complete therapy) by reducing occlusion. Although several of the PICC line studies that we reviewed used heparin doses that were similar to those used in the umbilical artery studies and demonstrated similar efficacy, the 9th American College of Chest Physicians consensus conference on antithrombotic therapy for neonates with central venous access devices (PICC lines) recommended maintenance of catheter patency through the use of unfractionated heparin at a continuous infusion rate of 0.5 IU/kg/hr, which would provide a total daily dose of 12 IU/kg/day. For neonates with umbilical artery catheters, they suggested prophylaxis with a heparin concentration of 0.25–1 IU/ml, which they suggest should yield a total daily heparin dose of 25–200 IU/kg/day to maintain patency [25]. Given the theoretical arguments that PICC lines may be at increased risk, it seems somewhat counterintuitive to recommend a lower dose for these lines. Thus, given a reasonable level of consensus derived from other PICC line studies, we feel that developing a separate set of recommendations for different types of lines is not supported by the literature and would be clinically confusing and therapeutically unnecessary.

After reviewing the literature, we sought to develop a unified, practical approach towards prophylactic heparin dosing that would take into account the above data, minimize risk and optimize efficacy. As seen in Table 3, the neonatal studies naturally divide into two groups, which we can define as high (~80–200 IU/kg/day) and low dose regimens (< 50 IU/kg/day). Both doses have shown efficacy and neither has been associated with significant adverse effects. In an effort to optimize efficacy while minimizing risk, we conclude that the lower total daily dose of between 10 and 50 IU/kg/day (0.5–2 IU/kg/hr) would best meet these needs. Of note, the American College of Chest Physicians recommended a daily dose of 12 IU/kg/day for PICC line prophylaxis and a daily heparin dose range of 25–200 units/kg per day for umbilical artery prophylaxis. Both of these recommendations are consistent with our recommendation of 10 to 50 IU/kg/day, although they overlap at different ends of the spectrum.

We then devised a practical clinical aid which calculates the heparin exposure infant weights from 500 to 4000 g, at infusion flow rates ranging from 0.5 to 4 ml/hr with continuous heparin infused at three different dosing regimens: 0.5 IU/ml, 0.25 IU/ml, and 0.5 IU/kg/hr in order to facilitate easy bedside determination as to what combination best meets the recommendations. [These recommendations have been consolidated in a table which is available on request from the corresponding author.]

METHODOLOGICAL LIMITATIONS

Of note, all of these studies are characterized by heterogeneity in both methodology and endpoints, thus precluding definitive meta-analyses of the effect of heparin on the longevity of long indwelling lines. Most studies confined themselves to the first catheter, while others used the same initial randomization for several catheters.

Study endpoints can be confusing as well. Line longevity has been studied and defined either as the presence or absence of line occlusion or the ability to infuse through the line for the prescribed duration for which it was intended. While sometimes overlapping, these endpoints can at times be quite different, for example when a line is electively removed for completion of therapy.

Furthermore, only one study compared different dosages, and no studies compared different types of lines. Thus, any unified recommendations must cull and combine data derived from different studies.

SUMMARY OF EVIDENCE AND CONCLUSIONS

Although many aspects of long line heparinization in neonates remain controversial, we believe that this review resolves several important issues and brings them to a new, unified and practical clinical application. Most importantly, there are quite definitive data indicating that heparinization decreases catheter occlusions without increasing intraventricular hemorrhage or other adverse effects based mostly on high quality randomized controlled trials. However, there is no decrease

in thrombi formation and the data on sepsis remain inconclusive. Additional studies are needed to further clarify and define these issues.

Whether or not prolonging catheter usability justifies adopting a therapy with minimal toxicity is subject to judgment/opinion. However, assuming that one does accept this premise, clinicians need a practical therapeutic approach while awaiting supplementary data. As such, we next suggested an optimal dosing schedule based on our review. We recommend that heparinization of long lines be based on the total daily dose of heparin; we suggest that a dose of between 10 and 50 IU/kg/day would provide therapeutic efficacy while minimizing toxicity. Finally, given that we found no significant differences in the therapeutic responsiveness of PICC lines vs. umbilical lines, we suggest that a universal recommendation for all types of long line prophylaxis in neonates would facilitate greater ease of use and increase acceptance. In summary, we have reviewed existing data and "re-packaged" it to provide a new, practical and unified clinical approach.

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References

1. Revel-Vilk S, Ergaz Z. Diagnosis and management of central-line-associated thrombosis in newborns and infants. *Semin Fetal Neonat Med* 2011; 16: 340-4.
2. Thornburg CD, Smith PB, Smithwick ML, Cotten CM, Benjamin Jr DK. Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters. *Thromb Res* 2008; 122: 782.
3. Barrington KJ. Umbilical artery catheters in the newborn: effects of heparin. *Cochrane Database Syst Rev* 2010; 2 doiI:10.1002/14651858.CD000507
4. Ankola PA, Atakent YS. Effect of adding heparin in very low concentration to the infusate to prolong the patency of umbilical artery catheters. *Am J Perinatol* 1993; 10: 229-32.
5. David RJ, Merten DF, Anderson JC, Gross S. Prevention of umbilical artery catheter clots with heparinized infusates. *Dev Pharmacol Ther* 1981; 2: 117-26.
6. Rajani K, Goetzman B, Wennberg RP, Turner E, Abildgaard C. Effect of heparinization of fluids infused through an umbilical artery catheter on catheter patency and frequency of complications. *Pediatrics* 1979; 63: 552-6.
7. Horgan MJ, Bartoletti A. Effect of heparin infusates in umbilical arterial catheters on frequency of thrombotic complications. *J Pediatrics* 1987; 111: 774-8.
8. Bosque E, Weaver L. Continuous versus intermittent heparin infusion of umbilical artery catheters in the newborn infant. *J Pediatrics* 1986; 108: 141-3.
9. Randolph AG, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials. *BMJ* 1998; 316 (7136): 969-75.
10. Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. *Cochrane Database Syst Rev* 2008; (2): CD002772. doi: 10.1002/14651858.CD002772
11. Shah PS, Kalyn A, Satodia P, et al. A randomized, controlled trial of heparin versus placebo infusion to prolong the usability of peripherally placed percutaneous central venous catheters (PCVCs) in neonates: the HIP (Heparin Infusion for PCVC) study. *Pediatrics* 2007; 119: e284-91.
12. Birch P, Ogden S, Hewson M. A randomised controlled trial of heparin in total parenteral nutrition to prevent sepsis associated with neonatal long lines: the Heparin in Long Line Total Parenteral Nutrition (HILLTOP) trial. *Arch Dis Child Fetal Neonat* 2010; 95: F252-7.
13. Kamala F, Boo NY, Cheah FC, Birinder K. Randomized controlled trial of heparin for prevention of blockage of peripherally inserted central catheters in neonates. *Acta Paediatr* 2002; 91: 1350-6.
14. Klenner AF, Fusch C, Rakow A, et al. Benefit and risk of heparin for maintaining peripheral venous catheters in neonates; a placebo controlled trial. *J Pediatr* 2003; 143: 741-5.
15. Uslu S, Ozdemir H, Comert S, Bolat F, Nuhoglu A. The effect of low-dose heparin on maintaining peripherally inserted percutaneous central venous catheters in neonates. *J Perinatol* 2010; 30: 794-9.
16. Isemann B, Sorrels R, Akinbi H. Effect of heparin and other factors associated with complications of peripherally inserted central venous catheters in neonates. *J Perinatol* 2012; 32: 856-60.
17. Tang J, Li XH, Wang H, Xiong Y, Mu DZ. Administration of low-dose heparin in total nutrient admixture prevents central venous catheter-related infections in neonates. *Zhongguo Dang Dai Er Ke Za Zhi* 2009; 11: 983-5.
18. Unal S, Ekici F, Cetin I, Bilgin L. Heparin infusion to prevent umbilical venous catheter related thrombosis in neonates. *Thromb Res* 2012; 130: 725-8.
19. Thornburg CD, Smith B, Smithwick ML, Cotton M, Benjamin D. Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters. *Thromb Res* 2008; 122: 782-5.
20. Chang GY, Lueder FL, DiMichelle DM, et al. Heparin and the risk of intraventricular hemorrhage in premature infants. *J Pediatr* 1997; 131: 362-6.
21. Warkentin TE, Levine MN, Hirsch J, et al. Heparin-induced thrombocytopenia in patients treated with low molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; 332: 1330-5.
22. Lesko SM, Mitchell AA, Epstein MF, et al. Heparin use as a risk factor for intraventricular hemorrhage in low-birth-weight infants. *N Engl J Med* 1986; 314: 1156-60.
23. Malloy MH, Cutter GR. The association of heparin exposure with intraventricular hemorrhage among very low birth weight infants. *J Perinatol* 1995; 15: 185-91.
24. Moclair A, Bates I. The efficacy of heparin in maintaining peripheral infusions in neonates. *Eur J Pediatr* 1995; 154: 567-70.
25. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schunemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis. 9th edn. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: 7-47S.

"The truth isn't always beauty, but the hunger for it is"

Nadine Gordimer (1923-2014), South African writer, political activist and recipient of the 1991 Nobel Prize in Literature. Gordimer's writing dealt with moral and racial issues, particularly apartheid in South Africa. She was active in the anti-apartheid movement, joining the African National Congress during the days when the organization was banned. She was also active in HIV/AIDS causes

"You never really understand a person until you consider things from his point of view... Until you climb inside of his skin and walk around in it"

Harper Lee (1926-2016), American novelist widely known for her novel *To Kill a Mockingbird*, which won the 1961 Pulitzer Prize and has become a classic of modern American literature